Right Lower Quadrant Pain in Young Patients with Leukemia

A Surgical Perspective

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A retrospective review of cecal and appendiceal complications occurring in young patients with acute leukemia since 1969 was performed. The objective of this study was to determine the relative incidence of appendicitis and typhlitis among patients with acute leukemia who had operation or autopsy in this institution as well as to determine the risks of operative intervention. Fifteen patients with these complications were identified among the 400 patients with acute leukemia seen during this time period. Signs and symptoms of an acute abdomen were present despite immunosuppression. The incidence of sepsis at the time of presentation was 53%. Preoperative risk factors identified most frequently were coagulopathy and organ failure resulting from sepsis. Postoperative morbidity (25%) and mortality rates (8%) were related to the development of infectious complications. Appendicitis occurred in eight of the 15 patients studied, whereas typhlitis or its complications was found in seven patients. No preoperative factors could be found to differentiate typhlitis from appendicitis on clinical examination. It is suggested that operation can be safely performed in neutropenic patients who have acute right lower quadrant pain and signs of peritoneal irritation and may be the only effective way of differentiating appendicitis from typhlitis.

INCREASINGLY AGGRESSIVE CHEMOTHERAPEUTIC REGIMENS have brought about improved long-term survival rates of up to 60% in patients with acute lymphocytic leukemia.[1,2] These aggressive regimens expose the patients to complications and death related to bone marrow suppression and neutropenia with the attendant infectious complications. The mortality rate from gram-negative sepsis approaches 40%. In patients with polymicrobial sepsis with cancer, the mortality rate is 70%.[3]

Intra-abdominal and, specifically, right lower quadrant (RLQ) infectious complications often are the source of such sepsis.[4] The evaluation and treatment of these intra-abdominal infectious complications involve the surgeon. Evaluation is often difficult in these critically ill immunosuppressed patients. The otherwise straightforward evaluation of RLQ pain in a young patient is obscured by the patient's underlying disease or treatment.[5] The range of pathologic processes to be expected and the implications of signs and symptoms in these patients might differ from those of "normal" patients, therefore making clinical assessment difficult for the surgical consultant. Consideration of the risks of operation in such patients adds to the difficulty in management.[4-6]

We have reviewed our experience with RLQ complications in young patients having chemotherapy for leukemia in order to determine the incidence of typhlitis and appendicitis, relative to each other, and to assess the risks of operative intervention. We have also attempted to document the incidence of localized and diffuse abdominal pain exhibited by this group of patients. Additional diagnoses made in relation to abdominal pain were documented, as well as the incidence of laparotomies with normal findings.

Methods

Discharge diagnoses at the Clinical Center, National Institutes of Health (NIH), between 1969 and 1984 identified 400 patients admitted for acute leukemia (AL) that were between the ages of 3 and 21 years. Of this group of 400 patients, 129 sustained 135 episodes of documented abdominal pain. The diagnoses related to these episodes were based on clinical laboratory, radiologic, and/or pathologic results recorded in these charts. Ninety-six of these 129 patients had autopsies at this institution available for analysis. Sixteen of the patients

TABLE 1. *Leukemic Patients with Right Lower Quadrant Complications*

		Age	
	N	Range	(Median)
Group 1 (operation)	13	5–12	(12)
Group 2 (autopsy)	3	7, 10, 21	(10)

had RLQ pathologic conditions identified as cecitis, typhlitis, appendicitis, cecal or appendiceal perforation, and mesenteric adenitis. The records of these 16 patients were then reviewed for the status of the primary disease, initial symptoms and signs with the RLQ complications, hematologic values, radiologic findings, and initial microbiologic results with abdominal signs or symptoms. Charts were also examined to determine the drug therapy preceding this complication. Operative risk factors, defined as hemodynamic instability, coagulopathy, or respiratory failure, were evaluated. Indications for operation, operation performed, and operative findings, as well as operative complications and deaths, were recorded. The results reported in surgical pathology (13 patients) and autopsy reports (three patients) were evaluated. Minimum follow-up period was 14 months. Additional causes of abdominal pain documented in 113 patients were also recorded.

Results

Study Group

Of the 400 patients admitted with AL who were between the ages of 3 and 21 years, 129 (32%) had a total of 135 documented episodes of abdominal pain. Among the 129 patients, 16 (12%) had laparotomies for RLQ findings (Table 1). Thirteen patients had operation (group 1), and three (group 2) patients had their disease confirmed at autopsy. Ages were from 3 to 21 in the leukemic patients. Nine were male patients and seven were female patients. Eleven patients had acute myelogenous leukemia, and six had acute lymphocytic leukemia.

Eleven of the 16 patients with AL with RLQ findings had evidence of advanced disease, including positive

bone marrow aspirate findings or evidence of visceral involvement. Seven patients were seen during initial induction chemotherapy, six during re-induction therapy for relapse, and two while their disease was in remission. Median survival for patients operated on was 7 months after surgery (range: 1 week to 5 years). All patients studied at autopsy died within 1 month of presentation with RLQ symptoms or signs.

Clinical Findings

A total of 125 patients studied had documented abdominal pain. Among the 135 episodes of AL, 60 were localized and 75 were diffuse. In 11 of 16 patients with AL with cecal or appendiceal pathologic conditions, the pain was localized to the RLQ of the abdomen, whereas four others had diffuse abdominal pain. Thirteen of 16 patients had fever and chills, whereas 10 had nausea and vomiting. All operated patients had abdominal tenderness to palpation that was localized to the RLQ. Thirteen of the 16 had documented peritoneal signs (rebound, abdominal wall rigidity, or involuntary guarding). All patients operated on had peritoneal signs. In 14 of the 16 operated leukemic patients, their temperatures were greater than 39 C for 2 consecutive days. One patient with AL had a palpable RLQ mass documented.

Laboratory and Radiologic Findings

Eight of the 16 patients with AL had leukocyte counts less than 2,000/mL, and four had counts between 2,000 and 10,000/mL. Three counts were greater than 15,000/mL. Ten of the 15 patients with AL were at their nadir leukocyte count at the time of their presentation. In 10 of the patients with AL the platelet counts were less than 70,000/mL (Table 2).

In two patients with AL intraperitoneal free air was seen on chest roentgenograph. Nine of 15 patients had abdominal roentgenographs showing dilated small bowel or air fluid levels.

Eight young patients with leukemia had positive blood culture results, despite the use of multiple prophylactic or empiric antibiotics in 14 of the patients. Six patients had gram-negative organisms cultured from their blood, one patient had anaerobic sepsis, and one

TABLE 2. *Hematologic Status*

		WBC Count			At	Platelet Count
	N	<2000	2000–10,000	>15,000	Nadir	<70,000
Group 1	13	6	4*	3*	7	7
Group 2	3	2	1*	0	3	3

* Abnormal cells seen in smear of these patients.

TABLE 3. *Microbiology*

	N	Positive Blood Culture	Receiving Antibiotic Therapy
Group 1	13	5* (44%)	10
Group 2	3	3* (100%)	3

* Six of eight gram-negative enteric bacteria.

TABLE 5. *Pathologic Condition at Operation or Autopsy in Patients with Right Lower Quadrant Symptoms*

	N	Appendicitis	Typhlitis	Mesenteric Adenitis
Group 1	13	8	4	1
Group 2	3	0	3	0

patient had polymicrobial sepsis, including fungemia (Table 3).

Only one of the patients with AL was not receiving or had not recently received antineoplastic therapy at the time of presentation. Five of these patients were being treated with chemotherapy at the time of complication, whereas nine patients had received chemotherapy within the preceeding 20 days. Eight patients with AL had received steroids within 15 days.

Operative Risk Factors

In a retrospective assessment of the operative risk factors at presentation of patients with AL, 10 patients had a coagulopathy (protime, plasma thromboplastin time > control and/or platelet count < 70,000), four had hemodynamic instability (defined as hypotension [blood pressure < 90] and requiring treatment with the volume expansion and/or vasopressors), and one was in respiratory failure. Of the 13 patients with AL operated on, indications for operation included acute abdominal pain with peritoneal signs in 11 and a suspected intra-abdominal abscess in one. A total of fourteen laparotomies were performed in 13 patients with AL. Nine had simple appendectomies, two had appendectomies with drainages of abscesses, and two had right hemicolectomies. At operation six patients had simple appendicitis, two had perforated appendices, two had cecal perforation, two had evidence of localized abscess formation, and one had a diagnosis of mesenteric adenitis. In the 13 leukemic patients operated on, there was one death resulting from overwhelming continued sepsis. There was one re-operation for cecal perforation in a patient after appendectomy. There were three wound infections,

three cases of intra-abdominal sepsis, a single case of respiratory failure, and one wound dehiscence. All of these complications occurred among three patients. The leukemic patients for whom autopsies were performed all died with sepsis 2–14 days after the onset of symptoms (Table 4).

Pathologic Findings

Pathologic examination at either operation or autopsy revealed eight cases of appendicitis (two of these with leukemic infiltrates and one with an associated abscess) among the leukemic patients. Two had normal appendices with cecal edema, and five had cecal necrosis (two with associated intra-abdominal abscesses) consistent with typhlitis. One had mesenteric adenitis documented by culture and biopsy (Table 5).

Additional Causes of Abdominal Pain in Leukemic Patients

Of the 129 young patients with acute leukemias, there were 135 documented episodes of abdominal pain; 60 were localized and 75 were diffuse. Aside from the patients with RLQ findings previously described, the clinical or pathologic diagnosis assigned to the cause of the abdominal pain was varied (Table 6). These were based on clinical, laboratory, radiologic, or pathologic findings recorded in the medical records. Autopsies were done on 92 of these 129 patients at this institution.

TABLE 4. *Operative Deaths and Complications (Group 1)*

	Number of Patients
Wound infection	3
Intra-abdominal sepsis	3
Respiratory failure	1
Wound dehisence	1
Reoperation	1
Death	1
Total	13

TABLE 6. *Other Causes of Abdominal Pain in Young Patients with Acute Leukemia*

Cause	N
Drug-induced illeus or enteritis	6
Pancreatitis	17
Perforated viscus (other than cecum)	10
Parasite infestation	3
Graft vs. host disease	2
Pelvic inflammatory disease	2
Cholecystitis	2
Splenic rupture or abscess	3
Bowel obstruction resulting from leukemic infiltrates	2
Intussuception	2
No diagnosis given	9

Discussion

The purpose of this study was to determine the relative incidence of appendicitis and typhlitis among young leukemic patients at our institution. The incidence of appendicitis and typhlitis lesions among young leukemic patients was roughly equal in a review of operated or autopsied patients. In 400 patients seen over a period of 15 years at the NIH, acute appendicitis was identified in eight and cecal edema, necrosis, or perforation consistent with typhlitis was noted in seven. One had a laparotomy with normal findings with the diagnosis of mesenteric adenitis by biopsy and culture. Cecal edema alone was found in two of the eight patients with typhlitis. The true incidence of these lesions in this population probably is higher because of the presence of less severe cases of typhlitis that do not come to operation or autopsy. The estimated incidence of clinically significant and pathologically proven cecal and appendiceal complications has been determined in this study to be at least 4% among all leukemic patients between the ages of 3 and 21 years. Among patients with AL to be operated on who had RLQ pain, appendicitis or typhlitis can be expected with equal frequency and will be found in 26% of those with localized RLQ pain.

Leukemic patients who presented with significant RLQ symptoms had sufficient indications for operation and had signs of peritoneal irritation documented despite having advanced disease or having received chemotherapy or steroids. All patients in our study had significant fever. These RLQ complications produced the clinical picture of an acute abdomen. Thirteen of 15 patients who had these problems did so during induction therapy for their leukemia. The low incidence of laparotomies with normal results in this group of patients probably reflects their perceived high operative morbidity and mortality rates.

Many of these patients appeared to be poor operative risks because of coagulopathy and hemodynamic instability. The incidence of sepsis in these young leukemic patients was high (53%) and usually resulted from gram-negative organisms. This occurred despite the liberal use of antibiotics. One-third of the leukemic patients demonstrated signs of major organ failure related to their sepsis.

The most common reported cause of death in leukemic patients is from sepsis.[8] In a study of 89 cases of perforated appendicitis at Los Angeles Children's Hospital, only 6% of blood cultures had positive results compared with 53% of our young leukemic patients.[9] Septicemia in patients with leukemia has been reported to result in a 20–40% mortality rate.[8] Studies of leukemic patients with surgical complications have demonstrated the incidence of sepsis to be as high as 75%.[4]

Appendicitis and typhlitis, or their complications, appear to be associated with significant morbidity and mortality rates in leukemic patients.

The term typhlitis in this setting was first used by Wagner et al. in 1970.[10] It referred to a necrotizing colitis involving the cecum or the cecum and appendix and was found in leukemic children who were receiving therapy and were often in the terminal stages of their disease. Others have used the term neutropenic enteropathy or referred to these clinical pictures as the ileocecal syndrome.[7,11] In autopsy series, the incidence of these lesions ranges from 9.9 to 12%. Both appendiceal and cecal complications have been estimated as occurring with an incidence of approximately 5%.[4,12,13] Although occurring infrequently, appendicitis is associated with a high mortality rate in leukemic patients.[13–15]

The vaguely defined clinical diagnosis of typhlitis is difficult, and operative findings range from simple edema of the cecum to a frankly necrotic and perforated cecum.[10,12,13,16] Diagnosis of this disorder without pathologic examination is speculative and the differentiation from appendicitis is unclear.[17] The role of surgical management in appendicitis is clear. The role of surgical therapy in typhlitis is less well defined.[15,18,19] Recommendations for therapy range from nonoperative therapy to right hemicolectomy.[20–24] Pleas for nonoperative therapy are often based on the patient's poor outlook for survival because of his or her underlying disease, a fear of surgical complications, or even hopes that the patient will be able to localize a cecal perforation.[25,26] Although conservative therapy can be successful in some instances of typhlitis, there are no prognostic signs that differentiate it from appendicitis or that predict progression to cecal necrosis. A review of 65 cases of appendiceal and cecal complications in young (<30 years) patients with ALL reported in the medical literature in 13 articles show only two nonoperative survivors. Of 26 operated patients, there were 21 who survived for more than 30 days (Table 7). A well-described syndrome of cecal necrosis or perforation in immunosuppressed patients receiving therapy with steroids or chemotherapy can also occur.[27,28]

In our patients, appendectomy was performed with minimal complications. Progression of the appendicitis to perforation or abscess formation puts the patient at high risk for subsequent infectious complications, illness, and death. Despite the poor preoperative risk status of these patients in terms of coagulopathy and associated organ failure, most of the complications seen in the operated patients were thought to be directly related to the patients' susceptibility to infection. The risk to the patient from surgically treatable intra-abdominal sepsis appears greater than the risk of complications from the surgical exploration in this setting. We are in

TABLE 7. *Outcome of Surgical and Nonsurgical Therapy for Young Leukemic Patients with Appendicitis and Typlitis: Review of the Literature*

Institution	Operated Cases	Operated Survivors	Nonoperative Cases	Nonoperative Survivors (>30 Days)
University of Chicago[12]	1	0	7	0
Long Island Jewish Medical Center[28]	1	1	—	—
Childrens Medical Center, Seattle[17]	4	3	—	—
Walter Reed General Hospital[29]	—	—	1	0
Memorial Sloan-Kettering[5]	1	1	2	0
Childrens Hospital of Los Angeles[7]	3	2	8	0
Hadassah University Hospital[26]	—	—	1	0
Columbia-Presbyterian Medical Center[16]	4	3	1	1
Memorial Sloan-Kettering[25]	—	—	1	1
Childrens Hospital of Los Angeles[13]	3	3	7	0
Memorial Sloan-Kettering[4]	6	5	6	0
Brooke Army Medical Center[22]	2	2	—	—
St. Jude Hospital[18]	1	1	5	0
Total	26	21 (78%)	39	2 (5%)

agreement with Schaller, who noted "that the sickest patients are the ones about whom the surgeon tends to procrastinate yet they are also the patients who may benefit most from early operation."[29]

Our study cannot address the larger questions of the outcome of abdominal pain in the great number of neutropenic patients with cancer who did not come to operation or autopsy who may have these disorders in milder forms. The relative efficacy of operative and nonoperative therapy on outcome of these patients can only be addressed in a prospective evaluation of these patients. In our leukemic patients operated on, median postoperative survival was significant (7 months), thus allowing the patient's survival to be determined by his response to chemotherapy. We are initiating a prospective evaluation of neutropenic patients with abdominal pain that will attempt to determine factors relevant to outcome.

Documented abdominal pain occurred in 32% of the young leukemic patients seen during the study period. Of the 135 episodes, 60 were localized and 75 were diffuse. When the clinical diagnosis of the cause for abdominal pain is evaluated, it can be seen that most of such episodes will respond to supportive cause and do not require operation.

Typhlitis and appendicitis appear to be equally common in the young leukemic patient with RLQ signs of peritoneal irritation. The preoperative differentiation between these two problems is difficult, and one cannot be secure in recommending nonoperative treatment. The classical signs of peritoneal irritation can be found in these patients despite their neutropenia and immunosuppressed condition and have the same implications as in the nonleukemic patient. The greatest risk to these patients appears to be from progressive local and systemic infection. This series and review of the literature suggests that appropriate surgical treatment in terms of

drainage of purulent material and appropriate resection of compromised tissues should strongly be considered in young leukemic patients with these findings.

Summary

In this review of leukemic patients admitted at the NIH over a period of 15 years with cecal and appendiceal complications, we find that appendicitis and typhlitis ranging from cecal edema to necrosis were equal in incidence among patients with signs of RLQ peritoneal irritation. Despite substantial preoperative risk factors, including coagulopathy and organ failure, operation could be performed safely with adequate supportive measures. Sepsis was common at the time of presentation, occurring in 53% of our patients. There were no discernable factors that differentiated appendicitis from typhlitis before operation or before autopsy. Operative death and complications were related to the patients' susceptibility to infection. We believe that neutropenic patients presenting with RLQ findings of peritoneal irritation can be operated on safely. In addition, this may be the only effective way to differentiate appendicitis from typhlitis.

Acknowledgment

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